Measurement of Troponin and Natriuretic Peptides Shortly after Admission in Patients with Heart Failure – Does it Add Useful Prognostic Information: An Analysis of the Value of Endothelin Receptor Inhibition with Tezosentan in Acute Heart Failure Studies (VERITAS).

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Abstract (Word Count 250)

Objective: To investigate the added prognostic value of admission measurements of brain natriuretic peptides (BNP) and troponins in patients with acute heart failure.

Background: Plasma concentrations of BNP and troponin are often measured for diagnostic purposes when patients are admitted with heart failure. Their prognostic value when measured soon after admission is uncertain.

Methods: Multivariable prognostic models for death or any worsening heart failure (WHF) by 30 days; 30-day death or re-hospitalization for WHF; and 90-day mortality were constructed using baseline data from the Value of Endothelin Receptor Inhibition with Tezosentan in Acute heart failure Studies (VERITAS) including BNP and troponin-I.

Results: Of 1347 patients, the median (IQR) value of BNP was 422 (156-945) pg/mL and 855 (63%) had measurable troponin-I. By 30 days, 432 patients had died or experienced WHF. Clinical variables had only moderate predictive performance that was not substantially improved by BNP or troponin-I (c-indices 0.6528 and 0.6595). By 30 days, 150 patients died or were re-hospitalized for WHF. The c-index using clinical variables (0.6855) was not improved by adding biomarkers. By 90 days, 135 patients had died. The c-index for mortality was somewhat better than for composite outcomes (0.7394) but improved little with biomarkers (0.7461).

Conclusion: Routine clinical data recorded at the time of admission on patients with acute heart failure is poor at predicting recurrent admissions but somewhat better at predicting mortality. BNP or troponin measured at admission did not improve predictions; measurement closer to discharge, or of other novel biomarkers, might perform differently.

Key words: acute heart failure; prognosis; biomarkers; statistical models

Abbreviations and Acronyms

BNP= b-type natriuretic peptide

IDI= integrated discrimination index

IQR= interquartile range

LLOQ= lower limit of quantification

MR-proANP= midregional pro-atrial natriuretic peptide

NRI= net reclassification index

NT-proBNP= amino-terminal pro-BNP

VAS= visual analogue score

VERITAS= Value of Endothelin Receptor Inhibition with Tezosentan in Acute Heart Failure Studies

WHF= worsening heart failure

Introduction

The prognosis of patients admitted to hospital with acute heart failure remains generally but not uniformly poor [1;2]. Many patients will die or be re-admitted within 30-days but most will not. Stratifying risk could improve the planning and delivery of care. Identifying patients at high, short-term risk of readmission or death might reasonably lead to a delay in discharge or intensive post-discharge surveillance, either conventionally or with new remote monitoring technologies, provided such strategies can be shown to alter prognosis [3]. However, prediction has to be fairly accurate to make risk stratification of this already high-risk population worthwhile. If too many cases are missed (false-negative cases) then clinicians would have no confidence in the strategy. If prediction includes too many false-positive cases then this might prolong hospital stay unnecessarily. If this was not accompanied by an increase in bed capacity, healthcare systems would not cope.

Predictive models have been developed using data from patients with acute heart failure enrolled in surveys, registries, and clinical trials that provide insights into which characteristics are associated with an adverse outcome [4]. Although these analyses have identified several predictors of outcome, they also show that existing predictive models are not very accurate, especially for re-admissions. Such models are of limited clinical use for managing individual patients or for service redesign. Bio-markers might improve prediction but whether they add prognostic value to standard routine clinical variables for patients with acute heart failure has seldom been reported [2;5-13]. Accordingly, we took the opportunity to investigate the value of adding brain natriuretic peptide and troponins to conventional prognostic markers in a large multi-centre study of acute heart failure.

Methods

The goal was to create parsimonious multivariable prognostic models for three outcomes: (1) the composite of death, WHF during the hospital stay, or re-hospitalization for WHF through 30 days; (2) death or re-hospitalization for WHF through 30 days; and (3) death through 90 days. Readily available data gathered at baseline in the Value of Endothelin Receptor Inhibition with Tezosentan in Acute Heart Failure Studies (VERITAS) were used to create a basic predictive model[14]. The additional value of bio-markers, including B-type natriuretic peptides (BNP) and troponins, was then investigated.

Patients. Patients enrolled in VERITAS within 24 hours of hospital presentation with WHF sufficient to cause breathlessness at rest or on minimal exertion were included in this analysis. The patient's report of dyspnoea had to be supported by a respiratory rate of at least 24 breaths per minute as objective support of respiratory distress. The investigator's clinical diagnosis of heart failure had to be supported by at least two of the following four criteria: (1) an elevated concentration of BNP or amino-terminal pro-BNP (NT-proBNP), (2) pulmonary oedema on physical examination, (3) radiological evidence of pulmonary congestion or oedema, or (4) left ventricular systolic dysfunction (left ventricular ejection fraction [LVEF] <40% or wall motion index $\leq$1.2) and also had to have received intravenous diuretics. Plasma concentrations of natriuretic peptides were rarely available at the time of inclusion. Most patients were included based on criteria two and three. Exclusion criteria included cardiogenic shock, electrocardiographic ST segment elevation myocardial infarction, ongoing ischemia or administration of a thrombolytic agent, a systolic blood pressure $\leq$100 mg Hg in patients not receiving a vasodilator or $\leqq$120mm Hg in those receiving a vasodilator, haemoglobin

concentration ≤10 g/dL, serum creatinine concentration ≥2.5 mg/dL [to convert to μmol/L, multiply by 88.4]. Patients were randomized to receive intravenous tezosentan, an endothelin antagonist, or placebo. This did not influence any of the above outcomes and is not considered further in this analysis.

Thirty-two predictors were considered (Supplementary Table S1), based on data available in VERITAS and on clinical judgement informed by the results of previous analyses from other studies of acute heart failure. To this were added two biomarkers: BNP and troponins that were measured from plasma samples obtained just prior to study drug initiation and stored at -20^{o}C locally and shipped to a core laboratory where analyses were done [15]. As described previously, (14) plasma concentrations of BNP and troponin I were measured using commercially-available ELISA kits: Peninsula Laboratories, San Carlos, USA for BNP; Labmaster, Turku, Finland for troponin I. Troponin T was measured using an electrochemiluminescence immunoassay (Roche, Germany). The lower limit of quantification (LLOQ) reported by the laboratory (BioProof AG, Munich, Germany) was 0.041 ng/mL for BNP, 0.01 ng/mL for troponin T and as not applicable (all results > 0 reported) for troponin I. Because troponin I and T were highly correlated ($r=0.87$, $p<0.0001$) and a higher proportion of troponin T values were missing, troponin I was used for this analysis. Non-detectable values were set to 0.5 times the LLOQ for BNP and to 0.5 times the minimum reported value for troponin I prior to log transformation.

Statistical Analysis. Data are expressed as percentages for categorical data and as median and inter-quartile range for continuous data. The linearity of association between each continuously distributed predictor variables and each of the outcomes was assessed using restricted cubic

splines with 4 'knots' with a test of the significance of the non-linear terms [16]. Where the association was non-linear, a readily-interpreted transformation was chosen through examination of plots of the predicted log hazard ratio against the value of the predictor and changes in Akaike's Information Criterion. If little information was lost, the same transformation was used to model each outcome. A summary of the model forms chosen for each continuous predictor is shown in Supplementary Table S1.

We used multiple imputation [17] with a method that assumes multivariate normality (SAS PROC MI) to handle missing values. The imputation model included all covariates under consideration for the multivariable models. The ranges of imputed values were restricted to the ranges of the observed values. Ten imputation datasets were used. Parameter estimates were averaged across these datasets using Rubin's algorithm [18] (SAS PROC MIANALYZE).

We constructed two full models (one with and one without biomarker data) for each of the three outcomes that included all of the variables listed in Supplementary Table S1. Backwards selection in each of the imputed datasets was then used to reduce the number of predictors, with the criterion for retention set at $P<0.10$. Predictors that were significant in the majority of the imputed datasets (>5) were kept in each of the final models.

The prediction ability of the resulting models was evaluated by computing differences in c-statistics (c-indices) between models with and without the addition of biomarkers. Because multiple imputation was used with 10 imputations, the c-indices were calculated for each imputation dataset using Harrell's method [19] and then averaged using Rubin's algorithm in

PROC MIANALYZE. For each endpoint, c-indices and their difference are presented as bias-corrected estimates with corresponding 95% confidence intervals based on 200 bootstrap samples of the imputed data sets.

Results

Of 1448 patients enrolled in the VERITAS studies and eligible for analysis, 101 (7.0%) were excluded because they were enrolled more than 24 hours from admission, leaving 1347 patients for this analysis. No patient was lost to follow-up. Natriuretic peptides were rarely measured by investigators and contributed to inclusion criteria in only 287 patients (20%). For this analysis, BNP and troponins were assayed retrospectively on stored plasma. The median age of patients was 72 (IQR 63-79) years and 41% were women. Most patients were Caucasian (87%) and had a pre-existing diagnosis of heart failure (73%). The prevalences of COPD (19%), diabetes (48%), renal dysfunction (37%) and atrial fibrillation (27%) were substantial. The median heart rate was 82 (71-95) beats per minute and respiratory rate was 26 (24-28) breaths per minute. Median systolic blood pressure was 127 (115-144) mmHg. Left ventricular ejection fraction was reported only in 779 patients (54%) from measurements taken up to 12 months prior to admission and was therefore not considered in the model. At the time of randomization, 632 (47%) patients were receiving β-blockers, 711 (53%) ACE inhibitors, and 135 (10%) angiotensin II receptor.

Values for BNP were generally elevated, with a median value of 422 pg/mL, although 74 (5%) patients had values below the assay's LLOQ (41 pg/mL) (Figure 1a). Plasma troponin-I was measurable in 855 (63%) patients with a distribution that was highly skewed to the right (Figure 1b). By 30 days, 432 patients had reached the composite outcome of death, in-hospital WHF by

day 7 or had been readmitted for WHF, and 150 had died or been re-hospitalized for WHF. By 90 days, 135 patients had died. The impact of biomarkers on the consistency with which predictor variables were included in models for each outcome of interest is shown in Supplementary Table S1.

Predictors of the composite outcome of death, WHF or readmission for WHF at 30 days in univariable analysis are shown in Table 1. Excluding biomarker data, the multivariable model included age, heart rate, respiratory rate, systolic blood pressure, history of COPD, history of diabetes, history congestive heart failure (CHF), history of renal impairment, dyspnea severity by visual analogue score (dyspnoea VAS) at baseline, albumin, BUN, haemoglobin, and sodium. The resulting c-index (0.6528) suggested only moderate predictive performance. BNP did not add to the model and troponin-I added little information, increasing the c-index only to 0.6595 without significant differences in c-indices between models.

By 30 days, 150 patients had died or been re-hospitalized for WHF. Age, heart rate, systolic blood pressure, history of CHF, dyspnea VAS at baseline, albumin, BUN, haemoglobin, and sodium were independent predictors of this outcome (Table 2). The final model resulted in a c-statistic of 0.6855 which was not significantly improved by either biomarker. Ninety-seven patients were rehospitalized for WHF within 30 days. The risk of WHF hospitalization, given that the patient had not died, was associated with similar baseline characteristics but, again, neither troponin I nor BNP was predictive of this outcome.

By 90 days, 135 patients had died. Biomarkers showed a much stronger relationship to mortality than to composite outcomes on univariable analysis (Table 3). Excluding biomarkers, the

multivariable model identified age, heart rate, systolic blood pressure, history of COPD, history of vascular disease, dyspnoea VAS at baseline, white blood cell count (WBC), albumin, BUN, and sodium as significant predictors of mortality with an overall c-index of 0.7394. BNP did not provide further prognostic information. The addition of troponin provided a small improvement in the c-index to 0.7461 and displaced WBC count from the model. The difference in c-indices between the two models was not statistically significant.

Discussion

This and other models that attempt to predict 30-day morbidity and mortality amongst patients with acute heart failure based on standard clinical, biochemistry and haematology measurements have met with limited success. Typically, they report a c-index of about 0.65 which is only slightly better than the play of chance (0.5). Although the results may be highly statistically significant, this reflects the large number of patients studied rather than the predictive accuracy of the models. This lack of prognostic accuracy renders such models of little practical clinical use. We had hoped that measurement of biomarkers such as BNP and troponin would add substantially to the predictive power of clinical models but they did not, at least when measured shortly after admission. Biomarkers might not be able to improve prediction but could still simplify it, by replacing a large number of variables with just a few, which might be perceived as an advantage. However, this was not the case in the current analysis.

Natriuretic peptides have predicted adverse outcomes in other studies and settings. Indeed, in out-patients with chronic heart failure, NT-proBNP is often the single strongest predictor of a variety of relevant outcomes including hospitalisation for WHF and death [20;21]. Some studies of acute heart failure have found that natriuretic peptides provide incremental prognostic information to clinical models but others have not [2;5;22;23]. This might depend not only on the specific natriuretic peptide measured but also on study size, the type of population included, the timing of the measurement of biomarkers, what other variables are in the model, the outcome of interest and the statistical analyses employed.

Large studies provide high statistical power and may demonstrate strong statistical associations that, however, may not be relevant to clinical practice. Demonstrating a statistical association should only be considered a first step, subsequent to which techniques such as classification and regression tree (CART), net reclassification index (NRI) and integrated discrimination index (IDI) should be applied to determine practical value. Superficial analyses even on very large data-sets can be seductively deceptive. For instance, in 87,842 patients with acute heart failure in the Acute Decompensated Heart Failure National Registry (ADHERE), a positive test for troponin (about 6% of patients) predicted in-hospital mortality but more than 80% of deaths occurred amongst patients who were troponin negative [24;25].

Many studies report on the prognostic value of natriuretic peptides in patients presenting with acute breathlessness, many of whom do not have heart failure [9;10;26-29]. In this setting, a biomarker that identifies patients with a disease that carries a poor prognosis is likely to predict outcome. However, the biomarker may perform less well when the analysis is confined to patients in whom the diagnosis of heart failure is already known [9;12].

Serial measurements of natriuretic peptides suggest that values nearer discharge may be more closely associated with prognosis than those close to admission [23;30]. Conceptually, natriuretic peptides might be considered cardiac stress markers although, because they are cleared by the kidney, renal dysfunction is also a major determinant of their plasma concentration. BNP is therefore, to some extent, a measure of renal function and will complete with other variables associated with renal function in multivariable models. If all other measures of renal function are removed from the model, then BNP would predict outcome but it would not be clinically

sensible to take such an approach. At the time of admission, plasma concentrations of natriuretic peptides might be a useful measure of cardiac stress. Plasma concentrations will generally fall with successful treatment although whether measurements treatment should be used to guide therapy is controversial [31]. The final plasma concentration will reflect the residual stress in the system after implementation of effective treatment and could be considered a method of auditing the success of treatment [32]. A patient who initially has a plasma BNP concentration that is only modestly elevated but rises during admission may have a worse outcome than a patient who starts with a high level that falls in response to treatment. Measurement of natriuretic peptides on admission may help with diagnosis [9;27;28] but even though their plasma concentrations are statistically related to in-hospital mortality [24], this provides no practical prognostic information for individual patient care. However, pre-discharge measurements of biomarkers might be a guide to longer term outcomes [23;30].

The specific marker measured and the outcome of interest may be important. For instance, the Biomarkers in Acute Heart Failure (BACH) trial showed that MR-proANP measured in the emergency room in 1,641 patients with suspected heart failure (diagnosis confirmed in 35%) predicted mortality at 7, 30 and 90 days and appeared superior in this respect to NT-proBNP with BNP trailing a poor third [33]. On the other hand, for the composite of death or recurrent emergency consultation, BNP measured at the initial visit performed somewhat better than the other two natriuretic peptides. Other markers, such as pro-adrenomedullin [5;33] and copeptin [34] might be better at predicting short-term outcome, although this may not be specific for heart failure related events. High-sensitivity assays for troponin have been introduced since this trial was completed that have the ability to detect and quantify plasma concentrations of troponin in

almost all patients. It is possible that such an assay could detect patients with very low troponin levels who might have a good prognosis. This could increase the prognostic value of troponin measured at admission.

The significance of an elevated troponin may be somewhat different to that of an elevated BNP. Increases in troponin predominantly reflect cardiac myocyte damage with leakage of troponin across the cell membrane, reflecting cell damage and death. Myocardial infarction is often silent and silent infarcts may be more common in patients with heart failure because of damage to cardiac sensory nerves [35]. Some elevations in troponin at the time of admission for heart failure are likely to reflect recent coronary events but others may reflect global myocardial stress and accelerated myocyte apoptosis [11;36;37]. Because troponin may reflect the amount of cardiac damage leading to, or indeed caused by, the episode of acute heart failure, measurement at the time of admission might be expected to predict outcome, which it did to a modest extent in our analysis. Increases in troponin after admission may also confer an adverse prognosis [38]. Our data are consistent with other reports showing statistical associations between troponin and mortality. However, it is not clear that this translates into a practical value.

This and other analyses are consistent in showing that prognostic models are better at predicting death rather than morbidity. This may perhaps be because death is driven more by the biological processes measured in these models. Morbidity may be more influenced by factors such as patient education, social support, frailty, the relationship with healthcare staff, economic factors and local organization of health services [39]. In order to develop useful predictive models for

hospital readmission it may be necessary to include many variables that are not usually collected by cardiologists in clinical trials or surveys.

This analysis suggests that BNP and troponin measured at admission provide little or no extra information to variables collected in routine clinical practice. However, just because a marker is not independently related to prognosis does not mean that it is not a potential therapeutic target or a surrogate marker of improved outcome. Preventing an increase in troponin or ensuring that BNP falls with treatment might both improve outcomes [22] as suggested by the recent Relaxin in Acute Heart Failure (RELAX-AHF) study [40]. There are many roles for biomarkers other than predicting outcome. Indeed, their potential to change management decisions is of much greater importance. If the term 'biomarker' is extended to heart rate and rhythm, blood pressure, potassium and renal function, then biomarkers are already used routinely to guide contemporary medical management of heart failure [41]. However, controversy persists over the value of newer plasma biomarkers such as natriuretic peptides and troponin for guiding treatment of heart failure [31;42].

There are many limitations to our study. This was a clinical trial population. By protocol design, both low and very high risk patients were excluded. Many patients will have declined to participate and it is also likely that investigators decided not to include some patients even though they fulfilled the entry criteria. Accordingly, this is a selected group of patients. It is possible that the prognostic models would be more accurate in clinical practice that does not exclude patients at either extreme of risk, although it is in patients of intermediate risk where the assistance of tests may be most required [43]. Many other variables might have been collected.

Intuitively, models developed using discharge rather than admission data might be better able to predict post-discharge outcome. Surprisingly, this does not seem to be the case for routine clinical information, with discharge data adding little to that collected at admission [2;44]. However, this may not be the case for biomarkers [23;45]. Conversely, an earlier measure of BNP might have better reflected the patient's state at the time of admission and provided greater prognostic information. Although the biomarker measures must have been taken within 24 hours of admission for AHF, some measures may have been taken after administration of intravenous diuretics which may have affected them. Thus, the possible prognostic value of measures taken early in an AHF episode cannot be entirely dismissed. There were too few in-hospital deaths (53 in our analysis population) to investigate prediction of this outcome.

In conclusion, for patients with acute heart failure, conventional clinical assessments made shortly after admission are poor at identifying death or readmission by 30 days but somewhat better at predicting all-cause mortality by 90 days. Measurement of BNP and troponins at admission do not substantially improve prediction of any of these specified outcomes.

Figure legend

Figure 1. Distribution of baseline values for BNP (pg/mL, panel A), Troponin I (ng/ml, panel B).

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Table 1. Predictors of 30-day death, worsening heart failure, or rehospitalization for WHF

Predictor*	HR for a change of	Univariable models			Multivariable model without biomarkers			Multivariable model with biomarkers		
		HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
Age, y (cubic)†	79 vs. 63	1.30	(1.10, 1.54)	0.2504	1.27	(1.06, 1.52)	0.0283	1.21	(1.01, 1.44)	0.0946
BMI, kg/m^2	5	0.93	(0.86, 1.01)	0.0958						
Heart rate, bpm	5	1.02	(0.99, 1.04)	0.1805	1.03	(1.00, 1.06)	0.0573			
Respiratory rate, ≤24/min†	5	0.75	(0.55, 1.03)	0.0005	0.76	(0.55, 1.06)	0.0011	0.74	(0.53, 1.03)	0.0002
Respiratory rate, >24/min†	5	1.26	(1.12, 1.41)		1.26	(1.11, 1.42)		1.29	(1.14, 1.45)	
Systolic BP, mmHg	10	0.94	(0.90, 0.99)	0.0109	0.95	(0.91, 1.00)	0.0345	0.95	(0.90, 0.99)	0.0214
Hx of COPD	Yes/No	1.37	(1.10, 1.71)	0.0057	1.27	(1.02, 1.60)	0.0354	1.29	(1.03, 1.62)	0.0259
Hx of DM	Yes/No	1.35	(1.11, 1.63)	0.0022	1.31	(1.07, 1.60)	0.0084	1.30	(1.06, 1.59)	0.0115
Hx of IHD, PVD, or stroke	Yes/No	1.28	(1.04, 1.59)	0.0224						
Hx of Valve Disease	Yes/No	1.44	(1.15, 1.82)	0.0019						
Hx of CHF	Yes/No	1.40	(1.11, 1.77)	0.0041	1.22	(0.96, 1.55)	0.0965	1.22	(0.96, 1.55)	0.1002
Hx of renal impairment	Yes/No	1.67	(1.38, 2.02)	<.0001	1.30	(1.04, 1.62)	0.0229	1.26	(1.01, 1.58)	0.0388
dyspnea VAS, mm (cubic)†	79 vs. 50	0.91	(0.75, 1.10)	0.0745	0.89	(0.73, 1.09)	0.0662	0.88	(0.72, 1.08)	0.0736
Time from admission to randomization, h	1	0.99	(0.98, 1.01)	0.2959				0.99	(0.97, 1.00)	0.0721
ECG QRS interval, ms	10	1.03	(1.00, 1.06)	0.0268						
Albumin, g/L	5	0.82	(0.75, 0.90)	<.0001	0.86	(0.78, 0.95)	0.0042	0.85	(0.77, 0.94)	0.0025
Log2 BUN, mmol/L	Doubling	1.56	(1.38, 1.76)	<.0001	1.26	(1.08, 1.46)	0.0026	1.25	(1.07, 1.45)	0.0043
Creatinine, umol/L	10	1.07	(1.05, 1.10)	<.0001						
Hemoglobin, g/dL (cubic)†	14.62 vs. 11.89	0.68	(0.56, 0.82)	<.0001	0.80	(0.65, 0.99)	0.0080	0.80	(0.65, 0.99)	0.0063
Sodium, mmol/L	3	0.85	(0.79, 0.90)	<.0001	0.89	(0.83, 0.95)	0.0005	0.89	(0.83, 0.95)	0.0006
Log2 BNP, ng/ml	Doubling	1.06	(1.01, 1.11)	0.0274						
Log2 TnI, ng/ml	Doubling	1.03	(1.01, 1.06)	0.0038				1.03	(1.00, 1.05)	0.0276
Bias-corrected c-index (95% CI)					**0.6528 (0.6298, 0.6758)**			**0.6595 (0.6367, 0.6823)**		
Difference (95% CI)					**0.0067 (-0.0014, 0.0149)**					

* Variables that are not shown were not significantly related to this outcome on uni- or multi-variable analyses. †Non-linear association with outcome.

BMI= body mass index; BP= blood pressure; CHF= chronic heart failure; CI= confidence interval; COPD= chronic obstructive pulmonary disease; DM= diabetes mellitus; ECG= electrocardiogram; HR= hazard ratio; IHD= ischemic heart disease; PVD= peripheral vascular disease; TnI= Troponin-I; VAS= visual analogue score.

Table 2. Predictors of Death or re-hospitalization for worsening heart failure by 30 days

Predictor*	HR for a change of	Univariable models			Multivariable model without biomarkers			Multivariable model with biomarkers		
		HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
Age, y	10	1.20	(1.04, 1.39)	0.0104	1.25	(1.08, 1.44)	0.0024	1.25	(1.08, 1.44)	0.0024
BMI, kg/m^2	5	0.88	(0.76, 1.01)	0.0739						
Heart rate, bpm	5	1.03	(0.99, 1.08)	0.1278	1.05	(1.00, 1.10)	0.0328	1.05	(1.00, 1.10)	0.0328
Systolic BP, mmHg	10	0.89	(0.82, 0.96)	0.0026	0.92	(0.85, 0.99)	0.0355	0.92	(0.85, 0.99)	0.0355
Hx of Valve Disease	Yes/No	1.54	(1.05, 2.25)	0.0279						
Hx of CHF	Yes/No	2.19	(1.39, 3.45)	0.0007	2.13	(1.34, 3.37)	0.0014	2.13	(1.34, 3.37)	0.0014
Hx of renal impairment	Yes/No	1.68	(1.22, 2.32)	0.0015						
Hx of smoking	Yes/No	0.41	(0.17, 0.99)	0.0485						
Baseline dyspnea VAS, mm	10	1.08	(1.00, 1.16)	0.0411	1.08	(1.00, 1.16)	0.0456	1.08	(1.00, 1.16)	0.0456
ECG QRS interval, ms	10	1.05	(1.01, 1.09)	0.0282						
Albumin, g/L	5	0.78	(0.65, 0.93)	0.0074	0.83	(0.68, 1.01)	0.0678	0.83	(0.68, 1.01)	0.0678
Log2 BUN, mmol/L	Doubling	1.85	(1.52, 2.25)	<.0001	1.65	(1.33, 2.06)	<.0001	1.65	(1.33, 2.06)	<.0001
Creatinine, umol/L	10	1.10	(1.06, 1.13)	<.0001						
Hemoglobin, g/dL (quadratic)†	14.62 vs. 11.89	0.73	(0.58, 0.90)	0.0011	0.92	(0.72, 1.18)	0.0678	0.92	(0.72, 1.18)	0.0678
Sodium, mmol/L	3	0.79	(0.71, 0.88)	<.0001	0.83	(0.75, 0.93)	0.0014	0.83	(0.75, 0.93)	0.0014
Log2 BNP, ng/ml	Doubling	1.06	(0.98, 1.16)	0.1627						
Log2 TnI, ng/ml	Doubling	1.03	(0.99, 1.07)	0.1893						
Bias-corrected c-index (95% CI)					**0.6855 (0.6408, 0.7302)**			**0.6855 (0.6408, 0.7302)**		

*Variables (other than biomarkers) that are not shown were not significantly related to this outcome on uni- or multi-variable analyses. †Non-linear association with outcome.
BMI= body mass index; BP= blood pressure; CHF= chronic heart failure; CI= confidence interval; ECG= electrocardiogram; HR= hazard ratio; TnI= Troponin-I; VAS= visual analogue score.

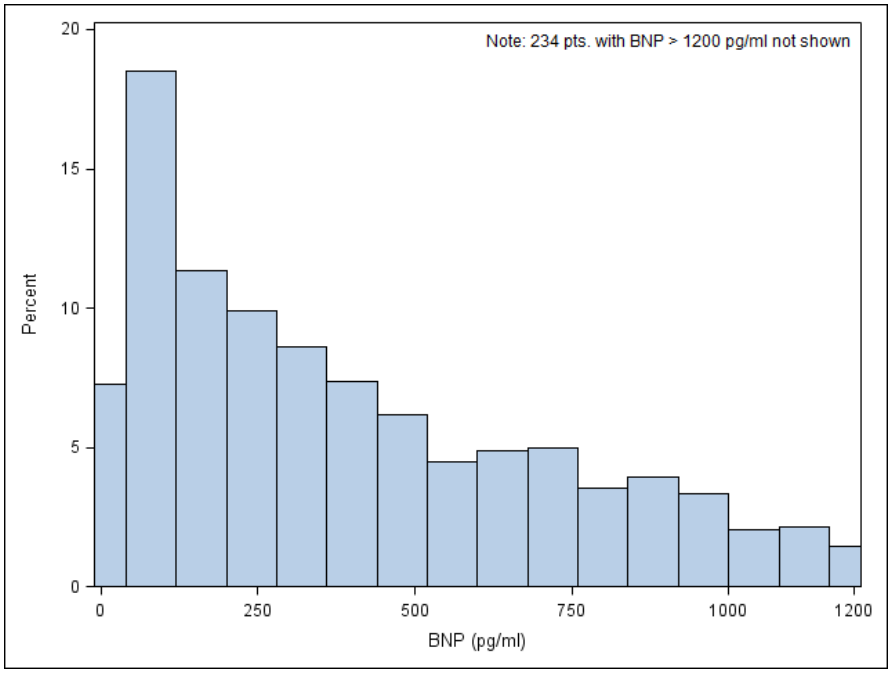
Table 3. Predictors of Mortality at 90 days

Predictor*	HR for a change of	Univariable models			Multivariable model without biomarkers			Multivariable model with biomarkers		
		HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
Age, y	10	1.53	(1.29, 1.80)	<.0001	1.46	(1.23, 1.72)	<.0001	1.42	(1.20, 1.69)	<.0001
White race	Yes/No	1.94	(1.02, 3.70)	0.0433						
BMI, ≤30 kg/m^2 † ‡	5	0.60	(0.46, 0.78)	0.0001						
BMI, >30 kg/m^2 † ‡	5	1.01	(0.77, 1.32)							
Heart rate, bpm	5	1.05	(1.00, 1.10)	0.0530	1.05	(1.00, 1.10)	0.0313	1.05	(1.00, 1.10)	0.0353
Respiratory rate, /min	5	1.17	(0.98, 1.40)	0.0849						
Systolic BP, mmHg	10	0.87	(0.80, 0.95)	0.0014	0.89	(0.82, 0.97)	0.0086	0.89	(0.81, 0.97)	0.0072
Hx of COPD	Yes/No	1.81	(1.25, 2.62)	0.0016	1.58	(1.08, 2.30)	0.0179	1.59	(1.09, 2.32)	0.0159
Hx of IHD, PVD, or stroke	Yes/No	2.04	(1.31, 3.17)	0.0016	1.75	(1.11, 2.76)	0.0169	1.60	(1.01, 2.54)	0.0451
Hx of Valve Disease	Yes/No	1.61	(1.08, 2.39)	0.0190						
Hx of renal impairment	Yes/No	1.81	(1.29, 2.54)	0.0006						
Dyspnea VAS, mm	10	1.08	(1.00, 1.17)	0.0427	1.08	(1.00, 1.17)	0.0495	1.08	(1.00, 1.17)	0.0570
WBC, 10^9/L	5	1.38	(1.15, 1.67)	0.0006	1.23	(1.01, 1.49)	0.0375			
Albumin, g/L	5	0.74	(0.62, 0.88)	0.0006	0.75	(0.62, 0.90)	0.0029	0.76	(0.63, 0.91)	0.0042
Log2 BUN, mmol/L	Doubling	1.79	(1.46, 2.21)	<.0001	1.52	(1.21, 1.90)	0.0003	1.52	(1.20, 1.91)	0.0004
Creatinine, umol/L	10	1.09	(1.05, 1.14)	<.0001						
Hemoglobin, g/dL	1	0.89	(0.81, 0.98)	0.0145						
Sodium, mmol/L (quadratic) †	141 vs. 136.4	0.84	(0.70, 1.00)	<.0001	0.88	(0.74, 1.05)	0.0074	0.84	(0.71, 0.99)	0.0019
Log2 BNP, ng/ml	Doubling	1.15	(1.05, 1.27)	0.0027						
Log2 TnI, ng/ml	Doubling	1.11	(1.06, 1.16)	<.0001				1.07	(1.02, 1.12)	0.0023
Bias-corrected c-index (95% CI)					**0.7394 (0.6988, 0.7800)**			**0.7461 (0.7072, 0.7851)**		
Difference (95% CI)					**0.0067 (-0.0085, 0.0218)**					

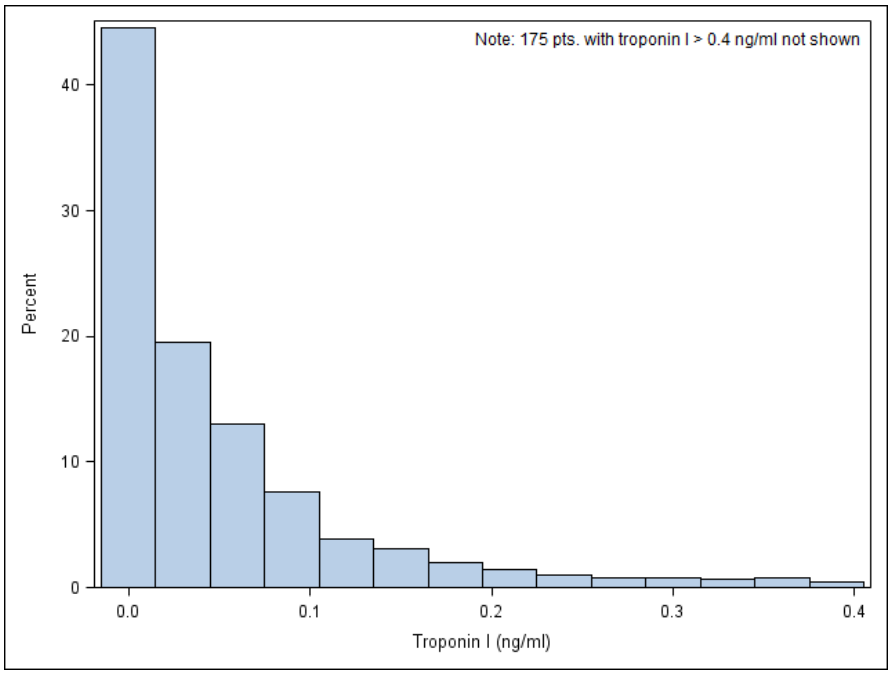
* Variables that are not shown were not significantly related to this outcome on uni- or multi-variable analyses †Non-linear association with outcome. ‡ risk falls as BMI rises towards 30. BMI= body mass index; BP= blood pressure; CI= confidence interval; COPD= chronic obstructive pulmonary disease; HR= hazard ratio; IHD= ischemic heart disease; PCI= percutaneous coronary interventions; PVD= peripheral vascular disease; TnI= Troponin-I; VAS= visual analogue score.

Figure 1. Distribution of baseline values for BNP (pg/mL, panel A), Troponin I (ng/ml, panel B).

a)



b)



Supplementary Table S1. Candidate predictors

Variable	N (% missing)	Prevalence (%) or Median & Quartiles	Sel. Freq. wo/w* Biomarkers M1†	Sel. Freq. wo/w* Biomarkers M2‡	Sel. Freq. wo/w* Biomarkers M3§	Transformation
Age, y	1347 (0%)	72 (63, 79)	10/8	10/10	10/10	Cubic polynomial for M1†.
Men	797 (0%)	(59.2%)	0/0	0/0	0/0	
White Race	1167 (0%)	(86.6%)	0/0	0/0	0/0	
BMI, kg/m^2	1274 (5.4%)	27.7 (24.6, 31.9)	0/0	0/0	3/4	Linear spline with one knot (nadir of risk) at 30 for M3§.
Heart rate, bpm	1346 (0.1%)	82.0 (71.0, 94.5)	8/3	10/10	10/9	
Respiratory rate, /min	1330 (1.3%)	26.0 (24.0, 28.0)	10/10	0/0	0/3	Linear spline with one knot (nadir of risk) at 24 for M1†.
Systolic BP, mmHg \	1332 (1.1%)	127 (115, 144)	10/10	10/10	10/10	
Hx of COPD	260 (0.1%)	(19.3%)	10/10	0/0	10/10	
Hx of DM	642 (0.1%)	(47.7%)	10/10	0/0	0/0	
Hx of IHD, PVD, or stroke	940 (0.1%)	(69.8%)	0/0	0/0	10/9	
Hx of Valve Disease	220 (0.1%)	(16.3%)	1/0	0/0	0/0	
Hx of CHF	981 (0.7%)	(73.4%)	7/7	10/10	0/0	
Hx of hyperlipidemia	472 (0.1%)	(35.1%)	0/0	0/0	0/0	
Hx of hypertension	1067 (0.1%)	(79.3%)	0/0	0/0	0/0	
Hx of renal impairment	500 (0.9%)	(37.5%)	10/10	0/0	0/0	
Hx of liver disease	105 (0.9%)	(7.9%)	0/0	0/0	0/0	
AF at admission	356 (0.9%)	(26.7%)	0/0	0/0	0/0	
Hx of smoking	102 (0.1%)	(7.6%)	0/0	0/0	0/0	
Hx of PCI or CABG	473 (0.1%)	(35.1%)	0/0	0/0	0/0	
Baseline dyspnea VAS, mm	1328 (1.4%)	66 (50, 79)	8/10	10/10	10/10	Cubic polynomial for M1†.
Admission to randomization, h	1347 (0%)	9.1 (4.6, 16.6)	4/7	0/0	0/0	

Variable	N (% missing)	Prevalence (%) or Median & Quartiles	Sel. Freq. wo/w* Biomarkers M1†	Sel. Freq. wo/w* Biomarkers M2‡	Sel. Freq. wo/w* Biomarkers M3§	Transformation
ECG QRS interval, ms	1338 (0.7%)	103 (84, 134)	0/0	0/0	0/0	
Sodium, mmol/L	1329 (1.3%)	139.0 (136.4, 141.0)	10/10	10/10	10/10	Quadratic polynomial for M3§.
BUN, mmol/L	1304 (3.2%)	8.2 (6.2, 11.3)	10/10	10/10	9/10	Log2-transform to reduce skewness.
Creatinine, umol/L	1344 (0.2%)	108.7 (88.4, 139.7)	0/0	0/0	1/0	
Albumin, g/L	1034 (23.2%)	38.0 (34.6, 41.5)	10/10	8/8	10/10	
ALT, U/L	1169 (13.2%)	18.6 (12.6, 29.4)	0/0	0/0	0/0	Log2-transform to reduce skewness.
Hemoglobin, g/dL	1346 (0.1%)	13.3 (11.9, 14.6)	10/10	10/10	0/0	Quadratic for M2‡ and cubic polynomial for M1†.
WBC, 10^9/L	1339 (0.6%)	9.0 (7.2, 11.4)	0/0	0/0	10/0	
BNP, pg/ml	1255 (6.8%)	422 (156, 945)	NR/0	NR/0	NR/0	Set zero to 0.5 x LLOQ for log2 transform.
Troponin-I, ng/ml	1254 (6.9%)	0.03 (0.00, 0.13)	NR/10	NR/0	NR/10	Non-detectable set to 0.5 x min for log2 transform.
Troponin-T, ng/ml	1223 (9.2%)	0.00 (0.00, 0.06)				Collinear with troponin-I.

∗Sel. Freq. w/wo = selection frequency out of 10 imputation datasets with and without addition of biomarker data. †M1= death, worsening heart failure or readmission for heart failure by Day 30. ‡M2 = death or readmission for heart failure by Day 30. § M3 = all-cause mortality by Day 90. \Systolic and Diastolic BP were highly collinear and latter was dropped from the model. AF= atrial fibrillation; BMI= body mass index; BP= blood pressure; CABG= coronary artery bypass surgery; CHF= chronic heart failure; COPD= chronic obstructive pulmonary disease; DM= diabetes mellitus; ECG= electrocardiogram; IHD= ischemic heart disease; LLOQ= lower limit of quantification; NR= not relevant; PCI= percutaneous coronary interventions; PVD= peripheral vascular disease.